REMARKS/ARGUMENTS

Prior to submission of this amendment, claims 31, 35-38, 40-47, 51-52 and 56-57, 59-61 were pending. Claims 1 and 40 have been amended to recite that the patient is human. Claims 1, 40, 60 and 61 have been amended as requested by the Examiner to correct various deficiencies in antecedent basis. Claim 59 has been amended to correct its dependency. Applicants expressly reserve the right to pursue any canceled matter in subsequent continuation, divisional or continuation-in-part applications. No new matter is added by this amendment.

Election/Restriction

The Examiner indicated that with respect to the further restriction requirement with respect to the additional genes listed in Claim 60, the restriction is maintained. In reply, Applicants again note that this claim depends from claim 31 and requires determining the expression level of additional RNA transcripts or products. Clearly if claim 31 is allowable, then claim 60 is allowable. There is not an undue burden on the examiner for searching purposes.

Applicant had elected CD44v6.

Drawings

The Office Action requests corrected drawings in compliance with 37 C.F.R. 1.121 (d).

Applicants submit herewith replacement sheets for Figures 1 – 2. Applicant request entry of the replacement sheets and withdrawal of this objection.

Rejection under 35 U.S.C. 112, first paragraph (enablement)

Claims 31, 35-39, 41-47, 51-52, 56-61 stand rejected under 35 U.S.C. 112, first paragraph as failing to comply with the enablement requirement. The claims allegedly contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. (page 3-4). The Office Action states that the specification does not provide enablement methods for determining the normalized level of LAMC2 or GPC3 in a sample and determining the normalized level of the corresponding genes products of LAMC2 or GPC3 in a sample.

The Legal Test for Enablement

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosure provided by applicants coupled with information known in the art at the time the invention was made, without undue experimentation [1] [2]. Accordingly, the test for enablement is not whether any experimentation is necessary, but whether, if experimentation is required, it is undue.[3] The mere fact that an extended period of experimentation is necessary does not make such experimentation undue [4] [5]

A finding of lack of enablement and a determination that undue experimentation is necessary requires an analysis of a variety of factors (i.e., the In re Wands factors). The most important factors that must be considered in this case include 1) the nature of the invention; 2) the level of one of ordinary skill in the art; 3) guidance provided in the specification, 4) the state of the prior art, and 8) the breadth of the claims.

"How a teaching is set forth, by specific example or broad terminology, is not important"[6] [7]. "Limitations and examples in the specification do not generally limit what is covered by the claims" MPEP § 2164.08. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. It is well settled that patent applicants are not required to disclose every species

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[1] MPEP §2164.0120

[2] *United States v. Telectronics, Inc.* 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1998)) *United States v. Telectronics, Inc.* 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1998))

[3] *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976)

[4] *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977)

[5] MPEP §2164.06.

[6] MPEP §2164.08

[7] *In re Marzocchi*, 439 F. 2d 220, 223-4, 169 USPQ 367, 370 (CCPA 1971)

encompassed by their claims, even in an unpredictable art. The legal standard merely requires that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed.[8]

Analysis

Applicants maintain that the claimed invention is fully enabled for the following reasons.

The Office Action states that the term "an EGFR inhibitor" is allegedly broad in that it includes every inhibitor in the class of EGFR inhibitors. The PTO agrees that the specification teaches the following EGFR inhibitors: Iressa, [agr]cyano-[bgr]methyl-N-[(trifluoromethoxy)phenyl]-propenamide (LFM-A-12, cetuximab, and Tarceva. The PTO states that the genus of EGFR inhibitors is expected to be very large. For example, the post filing date art of Giaccone allegedly teaches six EGFR inhibitors (Iressa, Tarceva, Ipatinib, cenertinib, ZD6474 an AEE788) (page 8) The specification allegedly does not teach which inhibitors are associated with the changes in the level of LAMC2 or GPC3 in colon cancer (page 7, 8). Thus it is allegedly unpredictable as to whether the results obtained for colon cancer using whichever EGFR inhibitor the inventor used could be extrapolated to other EGFR inhibitors because each inhibitor works by a different mechanism. (page 8).

Applicants note that the term "EGFR inhibitor" is defined in the specification at, for example page 12, to a molecule having the ability to inhibit a biological function of a native epidermal growth factor receptor (EGFR).

Applicants enclose a declaration by Joffre, B. Baker, PhD. Dr. Baker is one of the inventors of the application. In his declaration at paragraph 6, Dr. Baker states that the patients were treated with an EGFR inhbitor selected from the group, erlotinib, gefitinib, cytoximab, EMB72000, AEE788. In paragraph 9, Dr. Baker states that all the results presented in Example

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[8] *Enzo Biochem., Inc. v. Calgene, Inc.*, 188 F.3d 13 62 (Fed. Circ. 1999), at 1372 (quoting *In re* Vaeck, 947 F.2d 488, 496 (Fed. Cir. 1991)).

2 and Tables 3 and 4 of the application were the result of treatment with a variety of different EGFR inhibitors. Therefore it is his belief that the prognostic information obtained by overexpression of LAMC2 or GPC3 RNA transcripts or their products is applicable to treatment with the class of drugs called EGFR inhibitors which inhibit a biological function of a native EGFR.

Accordingly, Applicants have shown that the prognostic information obtained from the overexpression of LAMC2 or GPC3 RNA transcripts or their products are applicable to any EGFR inhibitor. Withdrawal of the rejection on this basis is respectfully requested.

The Office Action states that the term "corresponding gene products" is allegedly broad in that it includes every possible amino acid product which can be produced by the LAMC2 and GPC3 genes such as those that would be produced by LAMC2 and GPC3 nucleic acids having naturally and non-naturally occurring allelic, mutant and splice variants (page 5). The PTO states that the specification does not provide an example for determining the normalized level of gene products. Both LAMC2 and GPC3 are expected to be capable of producing several different gene products. While the wild type LAMC2 and GPC3 nucleic sequences were known in the prior art, this information allegedly does not allow one to envision all possible gene products, including allelic and splice mutants as well as homologous sequences.

First, applicants note that they have amended the phrase as requested by the PTO from "corresponding gene products" to "their products".

Second, Applicants note that the RNA transcripts or their products being detected by the methods of this invention are being obtained from the colon tumor tissue, they are not being generated synthetically. Accordingly, all RNA transcripts or their products being detected by the methods of this invention are native sequences from colon tumor tissue.

Secondly, Applicants note that one skilled in the art would understand the meaning of RNA transcripts and their products. The specification at page 15 describes methods for the isolation of total mRNA from tumor tissues. The specification at pages 15 – 20 describes methods for the detection of RNA transcripts from the mRNA isolated from the tumor tissues. One skilled in the art would understand that such RNA transcripts will include any native RNA

transcript such as mutant and splice variants of LAMC2 and GPC3. Applicants also note that the specification at page 21, paragraphs [0063-0064] describes methods of measuring the level of proteins in tumor tissue through immunology or proteomics. One skilled in the art would understand that the RNA transcript products are native proteins present in colon tumor tissue.

For these reasons, withdrawal of the rejection based on this reason is respectfully requested.

Finally, the PTO states that it is allegedly unpredictable as to whether the results obtained in human patients could be extrapolated to other organisms.

Applicants have amended the claims to recite that the patient is a human patient. Withdrawal of the rejection on this basis has been rendered moot and withdrawal is requested.

Rejection under 35 U.S.C. 112, second paragraph

Claims 31, 35-39, 41-47, 51-52, 56-61 stand rejected under U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 31, 35, 39, 41-47, 51-52, and 59-61 are allegedly indefinite over the recitation of the phrases "the normalized level" , "the predictive transcripts", and "the corresponding gene product". There is allegedly insufficient antecedent basis.

First Applicants note that the term "normalized level" is a modifier of the predictive RNA transcripts. Accordingly, there is no need for antecedent basis for the term. Secondly, the term "normalized level" is defined in the specification at, for example, paragraph [0028] refers to the level of the transcript or gene expression product relative to the mean levels of transcripts/products of a set of reference genes, wherein the reference genes are either selected based on their minimal variation across patients, tissues or treatments (housekeeping genes) or the reference genes are the totality of tested genes. In the latter case, which is commonly referred to as "global normalization", it is important that the total number of tested genes be relatively large, preferably greater than 50. Finally methods of normalization of gene expression

are described in the specification from page 24 to page 25, paragraph [0078]. Accordingly, the term "normalized level" is understood by one skilled in the art.

Applicants have amended the term "predictive transcript" in claims 31, 40 and 60 to read "predictive RNA transcript". Accordingly, there is now sufficient antecedent basis for this term.

Applicants have amended the term "corresponding gene product" in claims 31, 40 and 60 to be "their product". Accordingly, the objected word "corresponding" has been removed.

For the above reasons, withdrawal of the rejection of these claims on this basis is requested.

Claims 31, 35-39, 41-47, 51-52, and 59-61 are allegedly indefinite over the recitation of the phrase "the transcript". The claim previously refers to predictive RNA transcripts, but not predictive transcripts in general so it is allegedly unclear if these are the same or different.

Applicants have amended the term in claims 31, 40 and 60 to recite "predictive RNA transcripts". Withdrawal of this rejection is respectfully requested.

Claims 31, 35-39, 41-47, 51-52, and 59-61 are allegedly indefinite over the recitation of "corresponding gene product". "Corresponding" is allegedly not an art recognized term to describe the relationship between a RNA transcript and its gene product and because the term has not allegedly been clearly defined in the specification one of skill in the art allegedly would not understand the metes and bounds of this term. Additionally it is allegedly unclear what is the product of an RNA transcript, (i.e. a protein, a spice variant, a mature RNA product).

Applicants have amended the term "corresponding gene product" in claims 31, 40 and 60 to be "their product". Accordingly, the objected word "corresponding" has been removed. Withdrawal of this rejection is respectfully requested.

Claims 41-47 are allegedly indefinite in the recitation of the phrase "the level of predictive RNA transcript or expression product thereof". This is allegedly unclear because the claim previously referred to a product of the RNA transcript but not to an expression product.

Applicants have amended claim 41 to recite the level of predictive RNA transcript or its product. The objected to term "expression product" have been removed. Withdrawal of this rejection is respectfully requested.

Claim 43 is allegedly indefinite in the recitation of the phrase "about 500 to about 5000" as there is no art recognized definition for this phrase. It is unclear as to whether "about 500 to about 5000" refers to 499 to 5001 or if it refers to 400-5100. The scope of the claim cannot be determined.

It is well known that the term "about" is acceptable in claim language. As the court in *Ecolab Inc. v. Envirochem Inc.* 264 F. 3d 1358, 1367, 60 USPQ2d 1173, 1179 (Fed Cir. 2001) stated "like the term "about" the term "substantially" is a descriptive term commonly used in patent claims to "avoid a strict numerical boundary to the specified parameter". quoting *Pall Corp v. Micron Separations, Inc.* 66 F.3d 1211, 1217, 36 USPQ2d 1225, 1229 (Fed Cir. 1995). The Court in *Verve, LLC v. Crane Cams, Inc.* stated that expressions such as "substantially" are used in patent documents when warranted by the nature of the invention, in order to accommodate the minor variations that may be appropriate to secure the invention. Such usage may well satisfy the charge to "particularly point out and distinctly claim" the invention, 35 U.S.C. § 112, and indeed may be necessary in order to provide the inventor with the benefit of his invention." *Verve, LLC v. Crane Cams, Inc.*, 311 F3d 1116, 65 USPQ2d 1051 (FED CIR. 2002). "That some claim language may not be precise, however, does not automatically render a claim invalid" *BJ Services Co. v. Haliburton Energy Services, Inc.* 338 F.3d 1368, 67 USPQ2d 1692 (Fed Cir. 2003) quoting *Seattle Box Co. Inc. v. Indus. Crating & Packing Inc.* 731 F.2d. 818, 826 (Fed Cir 1984). The question becomes whether one of ordinary skill in the art would understand what is claimed when the claim is read in light of the specification. In *B.J. Serivces* the Federal Court held that the term "about" was not indefinite.

Applicants note that one skilled in the art would understand the scope of the phrase 'about 500 to about 5000 bases" with reference to the specification. The phrase refers to the length of the cDNA's present on an array. One skilled in the art would understand that the length of the cDNA's must be sufficient for specific hybridization to the predictive RNA transcript and be limited by the length of the specific gene transcript. One skilled in the art

would understand the microarray procedure being used and the effective length of cDNA's present on such an array. The phrase is not indefinite to one skilled in the art.

Claim 51 is allegedly indefinite in the recitation of the following phrases "said fixed paraffin embedded tissue", the "the presence of a protease" , "the lysis solution", "the wax solidifies", "the nucleic acid" and "said cooled lysis solution". There is allegedly insufficient antecedent basis for these limitations in the claims.

Applicants have amended claim 51 to recite the method of claim 35, wherein RNA is isolated from colon cancer cells present in a fixed, paraffin-embedded tissue by a procedure comprising: incubating one or more sections of said fixed, paraffin-embedded tissue at a temperature of about 56 °C to 70 °C in a lysis buffer, in the presence of a protease, without prior dewaxing, to form a lysis solution; cooling the lysis solution to a temperature where the paraffin solidifies; and isolating the RNA from said cooled lysis solution.

Applicants have clarified that the colon cancer cells of claim 31 are present in a fixed paraffin-embedded tissue. Applicants note that the phrase "presence of a protease" does not require antecedent basis since it is referring to "a protease". Applicants note that there is antecedent basis for "a lysis solution" in step (b), so that reference to "the lysis solution" in step (b) and "said lysis solution" in step (c) is proper. Applicants have amended the term "wax" to recite paraffin for which there is antecedent basis. Applicants have clarified the nucleic acid is ribonucleic acid (or RNA) for which there is antecedent basis. Withdrawal of this rejection is requested.

Claim 52 is allegedly indefinite in the recitation of the phrase "the use of a kit". The claim does not recite how the kit is to be used in the method of claim 31.

Applicants have amended claim 52 to recite the "further" use of the kit. Support for how to use the components of the kit can be found in the specification at for example, pages 14 to 20. Withdrawal of this rejection is respectfully requested.

Claim 56 is allegedly indefinite over the recitation of the phrases "the expression level", "the gene product" and "said subject" as there is allegedly insufficient antecedent basis for these limitations.

Applicants have amended claim 56 to recite in the preamble that the method uses the expression level of LAMC2 or GPC3. Accordingly, there is no antecedent basis for the phrase "the expression level". The term "gene products is recited in the preamble which provides antecedent basis for this phrase. The term "said subject" has been amended to recite "said patient" for which there is antecedent basis. Withdrawal of this rejection is requested.

Claim 57 is allegedly indefinite over the recitation "said subject". There is insufficient antecedent basis for this limitation.

The term "said subject" has been amended to recite "said patient" for which there is antecedent basis. Withdrawal of this rejection is requested.

Claim 59 is allegedly indefinite over the recitation of the phrases "said polynucleotides" and "said genes". There is insufficient antecedent basis for these limitations.

Claim 59 has been amended to depend from claim 41 which provides antecedent basis for "polynucleotides" and the reference to said genes has been deleted. Withdrawal of this rejection is requested.

Claim 60 is allegedly indefinite over the recitation of the phrases "the prognostic transcript", "the increased normalized level" and "the corresponding gene product". There is insufficient antecedent basis for these limitations. Claim 60 is also allegedly indefinite over the recitation of the phrase "the transcript". The claim previously refers to predictive RNA transcripts but not to predictive transcripts in general.

Claim 60 has been amended to provide correct antecedent basis for these phrases. Withdrawal of this rejection is requested.

Please direct any calls in connection with this application to the undersigned at the number provided below.

Please charge any additional fees, including additional fees for extension of time, or credit overpayment to Deposit Account No. **08-1641**, referencing Attorney's Docket No. **39740-0005A**.

Respectfully submitted,

Date: December 21, 2006

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